Table IV. Rate Data for the Uncatalyzed Hydrolysis of 2-Chloro-N-methylbenzohydroxamic Acid in the Presence of Salts at 90.0 °C

Salt	Concn, M	$10^6\ k_{\mathrm{obsd}}$[a]
NaCl	3.00	1.11
NaCl	6.31	1.94
NaBr	6.31	1.33

[a] Average first-order rate constant, s^{-1}.

their conjugate bases and the rate laws are best interpreted according to the mechanism of eq 3–5 for that range.

Specific salt effects[7] are expected at the high concentrations employed to maintain constant ionic strength in the alkaline hydrolyses. These effects are illustrated in Table IV. Note that the rate constants reported in Table IV are for reactions in the absence of any added hydroxide. Direct comparison of the rate constants in Tables III and IV is not possible since in one case the reaction involves the hydroxamic acid reacting with water and in the other its conjugate base reacting with hydroxide ion or water. These two cases involve different charge types; however, at the concentrations of catalytic acid or base employed in this study, there will be specific salt effects for all charge types.

Experimental Section

The N-methylbenzohydroxamic acids were synthesized by adaptation of the method used by Ulrich and Sayigh[13] for the preparation of N-methylacetohydroxamic acid. ^{1}H NMR and ir spectra are consistent with the structures listed. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

N-Methyl-2-methylbenzohydroxamic acid, crystallized successively from benzene and carbon tetrachloride, had mp 120–121 °C. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.72; N, 8.48. Found: C, 65.14; H, 6.48; N, 8.47.

N-Methyl-2-chlorobenzohydroxamic acid, crystallized as above, had mp 118–119 °C. Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.61; H, 4.38; N, 7.59.

N-Methyl-4-methylbenzohydroxamic acid had mp 119–120 °C dec (lit.[14] 122 °C).

Kinetic measurements were made by the spectrophotometric method reported previously[4] employing a Beckman DU spectrophotometer set at 520 nm for the 2-methyl- and 4-methyl-N-methylbenzohydroxamic acid runs and at 500 nm for the N-methyl-2-chlorobenzohydroxamic acid runs. The acidity of the $FeCl_3$ solution was adjusted as before[4] for the alkaline runs.

Pseudo-first-order rate constants were obtained from the slope of the appropriate graph[4] with numerical values computed by the method of least squares.

Each rate constant listed in Tables I, III, and IV is the average of two to five runs. Average deviation from the mean is less than 4.5%. Temperature control was ±0.1 °C. Initial hydroxamic acid concentrations were 0.01 M.

Registry No.—2-Methyl-N-methylbenzohydroxamic acid, 24962-87-6; 4-methyl-N-methylbenzohydroxamic acid, 1613-85-0; benzohydroxamic acid, 495-18-1; 2-chloro-N-methylbenzohydroxamic acid, 59686-63-4.

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Base-Catalyzed Hydration of α,β-Unsaturated Ketones

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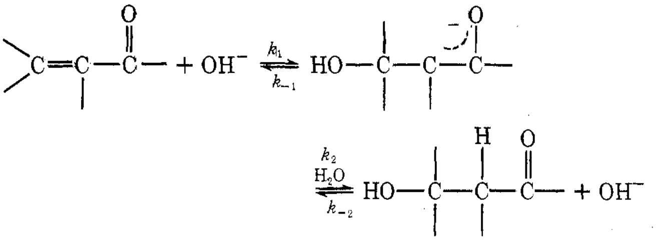
Homologues of 3-buten-2-one hydrate in dilute aqueous base to produce aldols, which in some cases undergo retro aldol condensation under the hydration conditions. Hydration of 3-buten-2-one proceeds with rate-controlling attack of hydroxide ion on C_4, $k_{H_2O}/k_{D_2O} = 0.6$, $\Delta H^{\ddagger} = 13.6$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -30.1$ eu. Hydration of 4-methyl-3-penten-2-one is 10^{-2} as fast and proceeds via rate-controlling proton transfer from water to C_3 of the enolate ion formed by attack of hydroxide ion at C_4 of the substrate, $k_{H_2O}/k_{D_2O} = 1.1$, $\Delta H^{\ddagger} = 15.2$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -25.6$ eu. Rates of hydration, dehydration, and retroaldol condensation were competitive for 3-penten-2-one and were calculated to be 7.6×10^{-3}, 2.3×10^{-3}, and 1.6×10^{-4} M^{-1} s^{-1}, respectively, at 40 °C. Equilibrium ratios calculated for the dehydration of aldols, [alkenone]/[aldol], show that dehydration is thermodynamically unfavorable for aldol condensation products of aliphatic aldehydes and ketones; kinetic measurements show the rate of dehydration to be comparable to or faster than the aldol condensation in many of these cases. Thus self-condensation of acetone (using a Soxhlet extractor) leads to the aldol product rather than the dehydration product for thermodynamic rather than kinetic reasons.

The acid-catalyzed hydration of α,β-unsaturated carbonyl compounds has received considerable study in recent years.[1–5] For a variety of aliphatic 3-alken-2-ones the hydration proceeds via a 1,4 addition of water to the conjugated C=C–C=O system followed by rate-controlling proton transfer to the enol thus formed. The hydration is characterized by a large solvent isotope effect (indicative of a primary isotope effect) and a large negative entropy (indicative of the covalent binding of a solvent molecule to the substrate prior to the rate-controlling step). The change in rate with acidity shows the carbonyl group to be significantly protonated in acidities beyond 4–6 M $HClO_4$.[5] The pK_a's of several α,β-unsaturated compounds have been measured recently and found to be adequately described by the Bunnett–Olson treatment.[6]

Studies of base-catalyzed hydrations are rare; apparently there are only two previous reports of base-catalyzed additions of water to α,β-unsaturated carbonyl systems. Fedor[4] has shown that 4-aryloxy-3-buten-2-ones hydrate in base via rate-controlling attack of hydroxide ion (Michael addition). This hydration is characterized by very small substituent effects ($\rho = 0.1$) and solvent isotope effects ($k_{H_2O}/k_{D_2O} = 0.94$). In a more limited study, Vik[7] has shown propenals to be hydrated in base with a large negative entropy of activation. Base-catalyzed hydration is thus seen to be a two-step process formally resembling a Michael addition (Scheme I).

Scheme I



The above results form a basis for reporting a study of the base-catalyzed hydration of the same 3-alken-2-ones for which the acid-catalyzed mechanism has been elucidated.[5] Of particular interest is determination of the rate-controlling step (k_1 or k_2) and elucidation of factors leading to a change in rate-determining step.

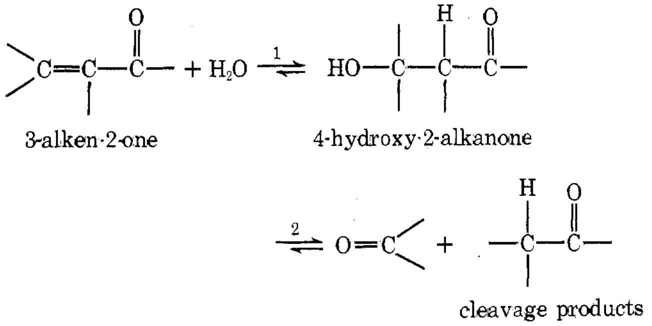
Experimental Section

All substrates were obtained from Aldrich Chemical Co. and were molecularly distilled just prior to each kinetic run. The general kinetic method (including calculation of rate constants for reversible reactions and calculation of activation parameters) was that described earlier.[8] Sodium deuterioxide solutions were made by diluting a 40% sodium deuterioxide solution (99% D, Stohler Isotope Chemicals) with deuterium oxide (99.8% D_2O, Stohler Isotope Chemicals).

Results

The reactions observed are reversible and at equilibrium the concentration of 3-alken-2-one is low (Scheme II).

Scheme II



Pseudo-first-order rate constants were measured spectrophotometrically in the traditional manner.[8]

Equilibrium ratios for step 1, [4-hydroxy-2-alkanone]/[3-alken-2-one], are known to be large from the earlier studies in acid solution.[5] Ratios vary from 3 to 20 depending on substrate and temperature (though exact comparisons cannot be made because of medium and acidity effects introduced by the rather concentrated acid solution required for acid-catalyzed hydration to occur at a convenient rate).[5] Equilibrium ratios for step 2, [cleavage products]^2/[4-hydroxy-2-alkanone], are also known to be large. For example, the equilibrium ratio is 20 for benzaldehyde + acetone and 10^4 for acetone + acetone (cleavage products identified). Because of (a) the squared concentration term in the numerator of the equilibrium ratio for step 2, (b) the low substrate concentration (spectral level, 10^{-4} M), and (c) the large magnitude of the equilibrium ratios for steps 1 and 2, the overall equilibrium in Scheme II lies almost totally (99.9%) to the right *when* the reverse aldol reaction (step 2) is kinetically important.

Experimentally, then, the observation is that about 5–10% of the reactant remains at equilibrium (similar to the acid-catalyzed hydration) for those cases where the reverse aldol condensation is not kinetically important whereas *no* reactant remains when it *is* kinetically important. Thus the conclusion is that reversible base-catalyzed hydration (step 1) occurs with 3-buten-2-one and 3-methyl-3-buten-2-one whereas a reverse aldol condensation (step 2) is predominant in determining the products of hydration of 4-methyl-3-penten-2-one. For 3-penten-2-one the two processes (steps 1 and 2) are competitive. The kinetic observations are a smooth pseudo-first-order *partial* disappearance of 3-buten-2-one and 3-methyl-3-buten-2-one, a smooth pseudo-first-order *total* disappearance of 4-methyl-3-penten-2-one, and a biphasic pseudo-first-order total disappearance of 3-penten-2-one.

Thus

$$k_{\text{obsd}} = k_{\text{hyd}} + k_{\text{dehyd}}$$
for 3-buten-2-one and 3-methyl-3-buten-2-one (1)

$$k_{\text{obsd}} = k_{\text{hyd}}$$
for 4-methyl-3-penten-2-one (2)

As eq 1 and 2 show, incursion of the reverse aldol condensation actually simplifies the measurement of rate of hydration by "draining off" the hydration product as formed.

Sorting out the experimental rate expression for hydration of 3-penten-2-one is somewhat more complex because of the biphasic nature of the rate plot. Early in the reaction (prior to attainment of steady-state concentration levels), the rate constant measured is essentially that expressed by eq 1 above. For the latter portion of the reaction, however, steady-state conditions apply and the appropriate rate expression is given by eq 3 (where k_2 is the rate constant for the reverse aldol condensation, step 2 of Scheme II).

$$k_{\text{obsd}} = \frac{k_{\text{hyd}} k_2}{k_{\text{dehyd}} + k_2} \tag{3}$$

All of the rate constants in eq 3 are calculable: k_{obsd} and $k_{\text{hyd}} + k_{\text{dehyd}}$ are measured experimentally; k_{hyd} and k_{dehyd} can be calculated from $k_{\text{hyd}} + k_{\text{dehyd}}$ and the equilibrium ratio. (Equilibrium ratio = $k_{\text{hyd}}/k_{\text{dehyd}}$ and was measured in the acid-catalyzed hydration study;[5] since the position of an equilibrium is independent of pathway, equilibrium ratios for acid- and base-catalyzed hydrations should be equal.) Thus for 3-penten-2-one in 0.10 N NaOH at 40 °C, $k_{\text{obsd}} = 5.0 \times 10^{-5}\ \text{s}^{-1}$, $k_{\text{hyd}} = 7.6 \times 10^{-4}\ \text{s}^{-1}$, $k_{\text{dehyd}} = 2.3 \times 10^{-4}\ \text{s}^{-1}$, $k_2 = 1.6 \times 10^{-5}\ \text{s}^{-1}$. The value of k_{dehyd} is probably smaller than calculated because of the medium effect on the measured equilibrium ratio; i.e., $k_{\text{hyd}}/k_{\text{dehyd}} = 3.35$ at 40 °C in 1.05 M $HClO_4$ but the ratio *increases* as acidity *decreases* (a medium effect).[5] The net conclusion is that k_{dehyd} and k_2 are of the same order of magnitude; however, k_{dehyd} *is* slightly the larger.

Subsequent discussion is based on values of k_{hyd} (Tables I and II) calculated from k_{obsd} using eq 1–5, as appropriate.

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{A_0 - A_e}{A_e} \tag{4}$$

[4-hydroxy-2-alkanone] = molarity of the hydration product at equilibrium; [3-alken-2-one] = molarity of the reactant at equilibrium; A_0 = absorbance at time zero (i.e., upon mixing); A_e = absorbance at equilibrium (i.e., at time "infinity").

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{k_{\text{hyd}}}{k_{\text{dehyd}}} \tag{5}$$

Table I. Values of k_{obsd} and k_{hyd} in Aqueous NaOH Solution[a]

N_{NaOH}	Temp, °C	$10^4\ k_{obsd} = 10^4\ k_{hyd}$
	3-Buten-2-one[b]	
0.010	30	2.67 (4.43)
	40	5.71 (9.4)
	50	11.5 (20.6)
	60	35.5
0.10	30	27.2 (48.4)
	4-Methyl-3-penten-2-one[c]	
0.50	50	4.43
1.00	40	3.87 (3.54)
	50	8.91 (7.18)
	60	17.9 (14.7)

[a] Means of replicate determinations, average deviations from mean values ≤±3%. Values in parentheses are for NaOD/D_2O solutions. [b] Followed at 220 nm. Equilibrium ratios (eq 4 and 5) are sufficiently large so that k_{obsd} and k_{hyd} are not meaningfully distinguishable. [c] Followed at 250 nm. See discussion of eq 2.

Table II. Values of k_{obsd} Equilibrium Ratios, and k_{hyd} in Aqueous NaOH Solution[a]

N_{NaOH}	Temp, °C	$10^4\ k_{obsd}$	[4-hydroxy-2-alkanone]/[3-alken-2-one]	$10^4\ k_{hyd}$
		3-Methyl-3-penten-2-one		
0.75	50	2.08	4.7	1.77
	60	3.80	9.0	3.40
	70	7.23	9.3	6.53
	80	13.6	12.7	12.0
0.50	40	1.94	6.6	1.68
	50	3.85	10.1	3.51
	60	7.80	7.0	6.83
1.00	30	1.88	13.5	1.75
	40	3.26	10.2	2.97
	50	7.72	9.4	7.01
		3-Penten-2-one[c]		
0.10	40	0.50		9.5
	50	1.1		21

[a] Means of replicate determinations; average deviations from mean value ≤±5%. [b] Followed at 240 nm. See eq 1, 4, and 5 for method of calculation. [c] Followed at 230 nm. See eq 1, 3, 4, and 5 discussion.

Table III. Activation Parameters for Base-Catalyzed Hydration of Alkenones[a]

Reactant	N_{NaOH}	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
3-Buten-2-one	0.010	13.6 ± 0.1	−30.1 ± 0.2
4-Methyl-3-penten-2-one	1.00	15.2 ± 0.5	−25.6 ± 1.6
3-Methyl-3-penten-2-one	0.25	13.8 ± 0.1	−33.1 ± 0.4
	0.50	13.9 ± 0.2	−31.5 ± 0.5

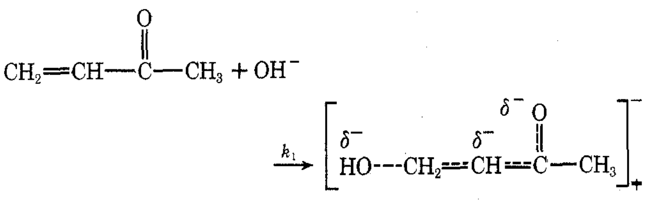
[a] Values calculated at 25 °C, ± standard deviation. Enthalpy and entropy of activation were calculated by a least-squares treatment of data in Tables I and II. Calculations were carried out on a CDC 3150 computer.

k_{hyd} = rate constant for step 1 (forward), Scheme II; k_{dehyd} = rate constant for step 1 (reverse), Scheme II.

Discussion

Hydration. The mechanism described by Scheme I is consistent with our data; either step may be rate controlling depending on substrate structure. The solvent isotope effect (k_{H_2O}/k_{D_2O} = 0.6) for the hydration of 3-buten-2-one indicates rate-controlling attack of hydroxide ion; the solvent isotope effect (k_{H_2O}/k_{D_2O} = 1.2) for the hydration of 4-methyl-3-penten-2-one indicates rate-controlling proton transfer from water to the enolate ion. The kinetically important step in the hydration of 3-buten-2-one is formally similar to a nucleophilic substitution reaction at carbon, as illustrated in Scheme III.

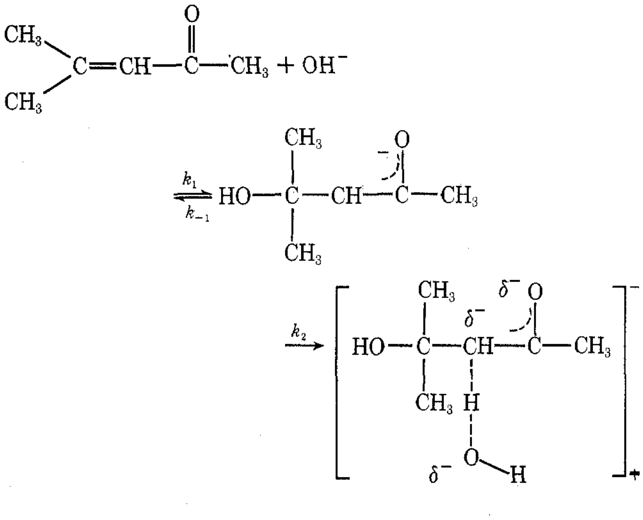
Scheme III



Dependent on transition state structure, Bunton and Shiner[10] have calculated a solvent isotope effect of 0.54–0.88. A value of 0.6 indicates maximum C–OH covalent interaction consistent with minimal negative charge on the incipient enolate oxygen. That is, the transition state is neither very "early" nor very "late". Although a solvent isotope effect of 0.6 for this general type of reaction appears to be the smallest yet observed, Pocker[11] reported a value of 0.67 for rate-controlling attack of hydroxide on the carbonyl carbon of 2-pyridinecarboxaldehyde; Jones[12] reported 0.75 for rate-controlling attack of hydroxide on the carbonyl carbon of ethyl acetate; Long[13] reported 0.86 for the SN2 reaction of hydroxide with an alkyl sulfonic ester.

The kinetically important steps in the hydration of 4-methyl-3-penten-2-one give rise to a solvent isotope effect composed of secondary *and* primary effects, as illustrated in Scheme IV.

Scheme IV



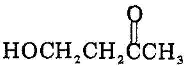
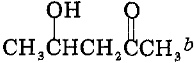
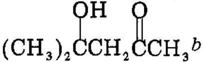
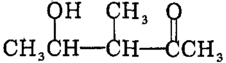
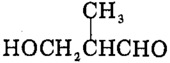
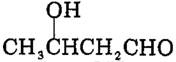
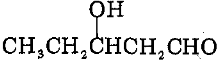
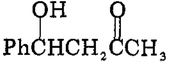
A Bunton–Shiner[10] calculation of the expected solvent isotope effect on the first step of Scheme IV (an equilibrium) yields k_{H_2O}/k_{D_2O} = 0.76, requiring a small isotope effect on the second step of about 1.6. Using the Bunton–Shiner procedure again on step 2 of Scheme IV produces a primary isotope effect of 2.3.[14] Though somewhat smaller than expected for such a proton transfer,[16] the value is reasonable considering the extended calculation required to produce it.

The change in rate-controlling step arises because of rather different effects on k_{-1} (Schemes I and IV) with substrate structural changes: k_{-1} is the rate constant for a process which may have many of the features of an SN1 reaction and thus when the leaving group (OH) is located on a tertiary carbon (4-methyl-3-penten-2-one), k_{-1} is much larger than when the leaving group is on a primary carbon (3-buten-2-one). An alternate picture of this process produces the same conclusion: the k_{-1} process produces an alkene and thus the most highly

Table IV. Solvent Isotope Effects for Base-Catalyzed Hydration of Alkenones

Reactant	$N_{NaOH} = N_{NaOD}$	Temp, °C	k_{H_2O}/k_{D_2O}
3-Buten-2-one	0.010	30	0.60
	0.010	40	0.61
	0.010	50	0.56
	0.10	30	0.56
4-Methyl-3-penten-2-one	1.00	40	1.1
	1.00	50	1.2
	1.00	60	1.2

Table V. Equilibrium Ratios for Dehydration of Aldols at Room Temperature[a]

Registry no.	Aldol	[alkenone]/[aldol]
590-90-9	 $HOCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$	0.05
4161-60-8	 $CH_3\overset{OH}{\overset{\|}{C}}HCH_2\overset{O}{\overset{\|}{C}}CH_3$[b]	0.25[5]
123-42-2	 $(CH_3)_2\overset{OH}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$[b]	0.11,[5] 0.06[9]
565-79-7	 $CH_3\overset{OH}{\overset{\|}{C}}H\text{—}\overset{CH_3}{\overset{\|}{C}}H\text{—}\overset{O}{\overset{\|}{C}}CH_3$	0.07
2134-29-4	$HOCH_2CH_2CHO$	0.1[7]
38433-80-6	 $HOCH_2\overset{CH_3}{\overset{\|}{C}}HCHO$	14[7]
107-89-1	 $CH_3\overset{OH}{\overset{\|}{C}}HCH_2CHO$	25[7]
59434-71-8	 $CH_3CH_2\overset{OH}{\overset{\|}{C}}HCH_2CHO$	50[7]
5381-93-1	 $Ph\overset{OH}{\overset{\|}{C}}HCH_2\overset{O}{\overset{\|}{C}}CH_3$	40[9]

[a] Last five entries measured at 25 °C, others at 30 °C. Ratios increase with increasing temperature. [b] Values taken from ref 5 in 2.57 M $HClO_4$ and thus incorporate a medium effect.

substituted (most stable) alkene is produced fastest.[18] The second step in Schemes I and IV, proton transfer from water to enolate ion (k_2 process), is much less sensitive to changes in structure at C_4 since this step of the reaction involves changes only at the incipient carbonyl group (C_2) and the carbon α to it (C_3). That is, k_2 for 3-buten-2-one and 4-methyl-3-penten-2-one are similar in magnitude. Thus for 3-buten-2-one $k_2 > k_{-1}$ whereas for 4-methyl-3-penten-2-one $k_2 < k_{-1}$. Other studies[4,7] have rather implicitly assumed $k_2 > k_{-1}$ (i.e., k_1 rate controlling) but it is not possible to establish the rate-controlling step apart from determination of the solvent isotope effect, since relative rates and activation parameters are inconclusive (Tables I–III).

Dehydration in the Aldol Condensation. It is widely recognized that the aldol condensation is synthetically useful for self-condensation of aldehydes or in those cases when a favorable equilibrium can be established by converting the aldol product to another; commonly dehydration of the aldol is convenient.[19] However, values of equilibrium constants for the dehydration process are scarce. Table V lists equilibrium ratios, [alkenone]/[aldol], for a variety of unsaturated aldehydes and ketones in aqueous solution. Of course these ratios are temperature and solvent dependent, but for the cases given in Table V equilibrium ratios increase somewhat with increasing temperature (i.e., raising the temperature favors dehydration). For condensation of aliphatic aldehydes and ketones with acetones, dehydration is thermodynamically unfavorable in aqueous solution. Dehydration of 4-hydroxy-2-pentanone, 4-methyl-4-hydroxy-2-pentanone,[9] and 4-phenyl-4-hydroxy-2-butanone[9] occurs faster than condensation of the respective aldehydes and ketones, but only for the latter case is the dehydration/hydration equilibrium favorable.

Acknowledgments. This research was supported by the Long Beach Heart Association and the California State University, Long Beach Research Foundation.

Registry No.—3-Buten-2-one, 78-94-4; 4-methyl-3-penten-2-one, 141-79-7; 3-methyl-3-penten-2-one, 565-62-8; 3-penten-2-one, 625-33-2.

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